The Effect of Guideline Implementation Strategies on Akathisia Outcomes in Schizophrenia

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ABSTRACT

Background: The purpose of this study was to examine the effect of a conceptually driven, multicomponent strategy for implementing guidelines to improve akathisia in schizophrenia.

Methods: Patients included in the study were recruited from 6 Veterans Affairs Medical Centers (VAMCs) that were split into geographically matched pairs with 3 VAMCs receiving basic education and 3 receiving enhanced intervention to promote guideline-concordant treatment and patient adherence.

Results: Of 293 patients with baseline and 6-month follow-up Barnes Akathisia Rating Scale (BARS) scores, results of both non-parametric and parametric repeated measures ANOVA showed several significant site-pair intervention effects, though the patterns were not consistent across the site-pairs. Logistic regression results controlling for baseline akathisia diagnosis and for patient covariates showed varying effects of the intervention among site-pairs as well. Exploratory results for differences in akathisia in those on novel versus conventional antipsychotics are also presented.

Conclusions: Akathisia tended to improve over time, but the enhanced guideline-implementation strategy did not consistently result in lower prevalence and severity of akathisia at all sites, apparently due to considerable differences in patient or site characteristics.

INTRODUCTION

Akathisia is a common side effect of treatment with antipsychotic medications, estimated to occur in approximately 20%-25% of patients with schizophrenia during acute treatment.[1] The term akathisia was first coined by Czechoslovakian neuropsychiatrist Ladislav Haškovec (1866-1944) and

refers to a drug-induced syndrome characterized by motor restlessness, a feeling of muscular quivering, and an inability to remain in a sitting position.[2] Because akathisia is a very disturbing adverse effect of antipsychotic medication, it is often associated with poor adherence to treatment and an increased risk of relapse.[3] The present study examines akathisia outcomes for patients with schizophrenia who participated in the Veterans Affairs-funded Schizophrenia Guidelines Project, which was a multisite study designed to examine how 2 different strategies to implement clinical practice guidelines for schizophrenia affect usual patient care and the outcomes of that care.

As 1 of 5 primary objectives for the overall project, the purpose of this study was to examine whether patients treated at sites receiving an enhanced guideline-implementation strategy would have a significant reduction in ratings of akathisia compared with patients treated at sites receiving only basic education about schizophrenia guidelines. In analyzing akathisia outcomes, the authors apply and briefly describe a recently published nonparametric analysis of variance (ANOVA) for repeated measures, alongside the familiar parametric repeated measures ANOVA. Given recent interest in comparing side-effect profiles of novel versus conventional antipsychotic medications,[4,5] the study authors also conducted ad hoc exploratory analyses to compare akathisia diagnoses at baseline and follow-up for patients treated with conventional versus newer antipsychotic medications.

METHODS
Schizophrenia Guidelines Project Overview

As described previously,[6] 8 eligible VAMCs within 4 Veterans Integrated Service Networks (VISNs) were selected to participate in the Schizophrenia Guidelines Project, conducted from March 1999 to October 2000. All of the VAMCs received basic education about schizophrenia guidelines. The present study utilizes data collected from patient interviews and from medical records at 6 VAMCs that completed the project: 2 sites within each of 3 Veterans Integrated Service Networks (VISNs). One of the 2 participating VAMCs per VISN was randomly selected to receive the enhanced intervention strategy and the other site within each pair received a basic education strategy for schizophrenia guidelines.

The enhanced intervention strategy, described in detail elsewhere,[7] consisted of using designated nurse coordinators at each intervention site to promote guideline-concordant prescribing by physicians and perform a clinical intervention with patients to improve medication adherence. Required human subjects approval was obtained from the designated institutional review board at each VAMC. Study personnel at the basic education sites included a site principal investigator (PI) and research assistant (RA). For the enhanced sites, personnel included (in addition to the PI and RA) a nurse coordinator who was responsible for conducting the enhanced intervention to improve guideline-concordant care.

Study Participants

Patient data were collected (from March 1999 to October 2000) for all consecutive eligible patients, age 18 to 65, who had an ICD-9 diagnosis of schizophrenia and were being treated for an acute exacerbation (increase in psychotic symptoms) in either inpatient or outpatient treatment settings at each VAMC. An acute exacerbation was defined for inpatients as an increase in psychotic symptoms (delusions, hallucinations, formal thought disorder, or bizarre behavior) documented in the medical record as justification for admission; and for outpatients as an increase in psychotic symptoms requiring a change in treatment.

Of 349 patients enrolled at the 6 VAMCs, 84% (n = 293) completed both baseline and 6-month follow-up assessments. Study participants lost to follow-up

were more likely to be white (45% vs. 28%, $\chi^2 = 5.8563$ df = 1; $P<0.05$) and unmarried/separated (95% vs. 84%, $\chi^2 = 4.1669$ df = 1; $P<0.05$), but there were no other significant demographic differences between those who did or did not complete follow-up interviews. The average time to follow-up interviews was 187 days (±31.5 days). Of the 349 patients, 291 had complete antipsychotic medication data available at both baseline and follow-up time-points, while 240 had both medication data and baseline and follow-up research interview data available.

Clinical and Demographic Measures

Baseline and Six-Month Follow-up Research Interviews. The site principal investigator and site RA were responsible for identifying eligible subjects at each site. The site PI was specifically responsible for verifying that patients met the diagnostic criteria for the study. Once the RA obtained informed consent, the RA interviewed each patient at baseline and 6-months later using a battery of instruments. Study participants received $20 compensation for each research interview completed.

The RAs were trained by the research team in Little Rock, Arkansas, in how to administer the research interview. RAs administered the Barnes Akathisia Rating Scale (BARS)[8] to assess akathisia, the Positive and Negative Syndrome Scale (PANSS)[9] to assess psychotic symptoms, and the Schizophrenia Outcomes Module (SCHIZOM)[10,11] to assess the process of care, patient characteristics, and outcomes of care including symptom severity, duration of illness, premorbid adjustment,[12] alcohol and substance abuse problems,[13] and medication adherence.[14, 15]

The BARS is one of the more commonly used scales for measuring akathisia in patients who are receiving antipsychotic drugs. It assesses both observed movements and the patient's subjective experience of restlessness. Global assessment is made on a scale of 0 to 5 with comprehensive defini-

tions provided for each anchor point: 0 = absent; 1 = questionable; 2 = mild akathisia; 3 = moderate akathisia; 4 = marked akathisia; 5 = severe akathisia. Reasonably good interrater reliability for the BARS has been reported. As suggested by the developer of the instrument,[8] the BARS global item score, which incorporates all the elements of the condition akathisia, provides an indication of overall severity and is relevant for most research and clinical purposes. A diagnostic threshold score of 2 or more indicates the presence of akathisia.[8]

Post-Intervention Chart Review. Pre-coded chart review instruments and instructions were developed by the research team and used by the site RAs to abstract medical record data for numerous domains related to patients' clinical status and service utilization. RAs also requested hard copies of medical records from any other VAMC patients visited, or non-VA providers seen by enrolled patients.

Data Analysis

Global item scores on the Barnes Akathisia Rating Scale[8] were compared for basic education and enhanced sites using several statistical approaches including nonparametric analysis for repeated measures, repeated measures ANOVA (parametric), and logistic regression analysis (for BARS diagnosis scores ≥2 versus <2) controlling for clinical and sociodemographic factors. For the BARS global item score responses, both a nonparametric and a parametric repeated measures ANOVA approach was employed, the reasoning being that the BARS response is not purely continuous in nature and showed non-normal distributions. If the familiar parametric model provides the same conclusions as the nonparametric, then one can reasonably assume that the violation of the parametric assumptions did not affect the conclusions that are made. This approach has been suggested by Conover[16] for situations such as this.

First, using the total sample of 291 patients who had complete baseline and fol-

low-up antipsychotic medication data (obtained by post intervention chart review), we compared the demographic and clinical characteristics of patients at basic education and enhanced sites (Table 1). To determine if there were site-pair differences at baseline among the three regionally matched site-pairs, we then compared the baseline patient characteristics for each of the 3 regional site-pairs separately (basic education versus enhanced). Because there were numerous baseline differences between the site-pairs (Table 2), and because outcome analyses for site-pairs indicated different patterns of significance, we chose to conduct the primary analyses for each site-pair separately.

Distribution of BARS Global Scores by Site-Pair. To examine change in the distribution of BARS global scores over time we selected the total number of patients (from n = 349), who had both baseline and follow-up BARS scores (n = 293) but not necessarily complete data on all covariates. This allowed for a maximal sample size of the available baseline and follow-up BARS data for initial comparisons. Because the majority of patients were rated as having no signs of akathisia (BARS global scores = 0), the BARS global scores were not normally distributed (Shapiro-Wilks tests for normality $P <0.0001$). Thus, for each site-pair, we examined the frequency distribution of BARS global scores by using both a parametric and nonparametric mixed model. Nonparametric analysis for repeated measures as described by Brunner, Domhof, and Langer[17] was used to test for group differences in the *distribution* of BARS responses over time. This method is useful for situations in which data are highly skewed or primarily ordinal in nature (as are the BARS global item ratings). We also used the repeated measures ANOVA (PROC Mixed procedure) in SAS[18] to test for group differences on mean BARS global item scores over time. By using a repeated measures mixed model and a parallel nonparametric model on the same data, we are essentially doing a sensitivity analysis to determine if

the conclusions about changes in the BARS responses are sensitive to departures from the classic normality assumption for repeated measures models. The nonparametric procedure tested the hypothesis that changes in the BARS global score *distributions* over time were identical for both the intervention and basic education groups. In a parallel fashion, the repeated measures ANOVA tested the study hypothesis that change in the BARS global item score means over time (follow-up from baseline) were identical for the enhanced and basic education groups. Stated another way, we are testing for a significant time by intervention interaction.

Modeling Improvement on BARS Akathisia Diagnosis. To examine factors associated with the presence of akathisia diagnoses controlling for other covariates, logistic regression analysis was used to fit 2 additional models, by site-pairs, for the 240 patients with complete baseline, follow-up, and covariate data. First, for each site-pair, change in the diagnosis of akathisia over time was examined (BARS global score ≥2) modeling the probability of no akathisia diagnosis at follow-up, and controlling for baseline akathisia diagnosis. Following methods described by Rosenbaum & Rubin,[19] we then computed similar logistic models that included a propensity score as an adjustment for covariates that might be related to receiving care at either basic education or enhanced intervention sites. The goal of such an approach is to obtain a minimally biased estimate of the difference in the treatment means in the presence of factors possibly related to receiving one of the treatment strategies. Propensity scores were calculated by using a logistic regression model with standard versus enhanced site location as the dependent variable. The propensity score model contained numerous covariates and traditional patient case-mix variables (age, race, etc.), and factors found to differ at baseline among any of the site-pairs (shown in Table 2). Specifically, the following patient covariates were included in the calculation of the propensity scores

Table 1. Patient Characteristics at Baseline

Parameter	All sites (n = 291) % (n)	Basic sites (n = 146) % (n)	Enhanced sites (n = 145) % (n)	*P*-Value (Fisher's % (n) Exact Test)
Race				
White	31 (89)	39 (57)	32 (22)	0.0022
Multiracial	69 (202)	61 (89)	78 (113)	
Gender				
Male	94 (273)	95 (138)	93 (135)	0.6362
Female	6 (18)	5 (8)	7 (10)	
Education				
Completed high school or less	55 (159)	59 (86)	50 (73)	0.1584
At least some college	45 (132)	41 (60)	50 (72)	
Marital status				
Not married/separated	85 (246)	83 (121)	86 (125)	0.5171
Married/living with someone	15 (45)	17 (25)	14 (20)	
Premorbid adjustment				
Poor	29 (84)	32 (46)	26 (38)	0.3656
Good	71 (207)	68 (100)	74 (107)	
Family history of mental illness				
Yes	57 (161)	55 (79)	59 (82)	0.4714
No	43 (121)	45 (65)	41 (56)	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	***P*-value**
Age	46.19 (7.84)	46.94 (7.95)	45.43 (7.67)	0.1003
Age illness onset—first MH visit	23.70 (7.01)	23.40 (6.19)	24.01 (7.76)	0.4665
Years since first MH visit	22.44 (10.13)	23.53 (9.80)	21.32 (10.36)	0.0632
Number of inpatient days past year)	13.64 (23.49)	20.05 (29.79)	7.19 (11.59)	0.0001

MH: mental health

for each site-pair: baseline BARS diagnosis, age, age at schizophrenia onset, premorbid adjustment (poor/good), race (African American/all others), inpatient versus outpatient status at enrollment in study, past year number of inpatient psychiatric hospital days, substance abuse (yes/no), baseline antipsychotic dosing (above versus within or below guideline range), and baseline adherence to antipsychotic medication (yes/no). Adherence to medication was operationalized using methods previously described,[7]

where either chart review documentation or patient self-report on the SCHIZOM indicated non-adherence. Patients were classified as having substance abuse problems if they responded positively to 1 or more CAGE questions (for alcohol or drugs) and reported substance use at least 1 to 2 days per week in the preceding 28 days. We operationalized guideline-concordant antipsychotic dosing according to recommendations suggested in clinical practice guidelines for schizophrenia.[20,21] For analy-

Table 2. Comparison of Patient Baseline Characteristics by Site-pairs (total n = 291)

Variable	Site-Pair 1			Site-Pair 2			Site-Pair 3		
	Basic (n = 40)	Enhanced (n = 61)	P-value	Basic (n = 47)	Enhanced (n = 50)	P-value	Basic (n = 59)	Enhanced (n = 34)	p-value
Age	47 (9.1)	45 (6.4)	0.1828	47 (8.1)	47 (7.5)	0.7296	47 (7.1)	43 (9.3)	0.0476
Age at onset	22 (5.7)	25 (9.3)	0.0352	25 (7.8)	23 (7.6)	0.2887	23 (4.7)	23 (4.2)	0.8988
Duration of illness (years)	25.5 (10.0)	20.1 (10.6)	0.0116	21.9 (10.2)	23.9 (10.1)	0.3349	23.6 (9.3)	20.0 (9.9)	0.0826
Race (% white)	40	16	0.0080	38	22	0.0797	39	32	0.5226
Race (% African American)	58	80	0.0131	57	78	0.0300	31	62	0.0033
Enrollment status									
(% inpatient)	90	77	0.0962	98	72	0.0004	92	56	0.0001
Number of inpatient days (past year)	37.5 (46.4)	7.0 (9.2)	0.0002	10.6 (11.2)	6.8 (9.5)	0.0759	15.8 (19.3)	8.1 (17.2)	0.0559
Premorbid adjustment (% good)	65	59	0.5458	72	78	0.5186	68	94	0.0035
Antipsychotic dose									
(% above guideline range)	30	25	0.5480	23	10	0.0755	19	29	0.2317
BARS akathisia diagnosis (% positive)	25	59	0.0008	47	32	0.1354	41	6	0.0003
PANSS total	66.1 (16.0)	82.6 (12.0)	0.0001	80.5 (10.0)	106.3 (17.2)	0.0001	78.2 (16.1)	64.4 (12.2)	0.0001
Medication adherence (% adherent)	53	43	0.3304	34	38	0.6850	42	65	0.0380
Substance abuse (% yes)	28	38	0.2885	38	26	0.1943	29	9	0.0238
Family history mental illness (% yes)	46	59	0.2081	50	64	0.1919	64	55	0.3526

ses presented here, the dosing variable was dichotomized to indicate patients who received doses above the recommended range versus those who were within or below range. To explore whether the ratings of akathisia were associated with guideline-concordant doses, a chi-square for both baseline and follow-up time points was computed.

Ad Hoc Analyses. Several ad hoc analyses related to novel versus conventional antipsychotic medications and the prevalence of akathisia diagnoses over time (using the total sample of 240 patients who had complete baseline and follow-up data) were also calculated. Chi-square tests were conducted for both baseline and follow-up time points separately to compare the BARS akathisia diagnoses between patients receiving conventional antipsychotic medications versus those receiving novel drugs. Twenty-one patients (of n = 240) were receiving polypharmacy at either time point (defined as receiving both a conventional and novel antipsychotic simultaneously) and were excluded from this analysis. Specific head-to-head drug comparisons were not possible for all of the drugs due to small sample sizes for many of the agents, but it was possible to compare the frequency of akathisia diagnoses for the two most commonly prescribed atypical drugs, risperidone (Risperdal) and olanzapine (Zyprexa), using chi-square analysis.

RESULTS
Sample
Demographic and clinical characteristics at baseline are presented in Table 1 for the total sample (n = 291) and for the three basic education sites (pooled, n = 146) versus the three enhanced intervention sites (pooled, n = 145). The majority of participants were male (94%), the mean age was approximately 46 years, 69% were multiracial (African-American primarily) and 31% were white. There were significant differences between basic education and enhanced sites overall in the distribution of

racial groups (with more multiracial patients enrolled at enhanced sites), and in the mean number of inpatient psychiatric hospital days over the past year (basic education mean = 20 and enhanced mean = 7).

Demographic and baseline clinical characteristics and comparisons for site-pairs are presented in Table 2. Significant differences in patient characteristics (basic education versus enhanced sites) were most notable at site-pair 1 and site-pair 3. Of the 3 site-pairs, site-pair 2 appeared to have the best matched patients at baseline, with only 3 of the covariates being significantly different.

Distribution of BARS Global Scores
The distribution of baseline and follow-up scores on the BARS global item for the basic education sites are shown in Figure 1. The point-prevalence estimate of positive BARS diagnoses was 38% (n = 56/146) at baseline and 22% (n = 25/112) at follow-up at the basic education sites. The distribution of baseline and follow-up scores on the BARS global item for the enhanced intervention sites are shown in Figure 2. The point-prevalence estimate of positive BARS diagnoses at enhanced sites was 37% (n = 54/145) at baseline and 23% (n = 30/128) at follow-up (see Figure 2).

The percentage of patients who had positive BARS akathisia diagnoses (total scores ≥2) are displayed in Figure 3 by site-pairs. There was substantial variation among sites in the frequency of positive akathisia diagnosis, ranging from 6% to 59% at baseline and from 6% to 47% at follow-up. Five of the 6 sites showed a reduction in akathisia diagnoses from baseline to follow-up, 1 site (pair 3 intervention site) showed no change.

As shown in Table 3, the effects of the intervention, time, and their interaction have a different pattern at each site-pair. According to the repeated measures ANOVA, there was a trend toward significant interaction at site-pair 1 ($P = 0.0872$),
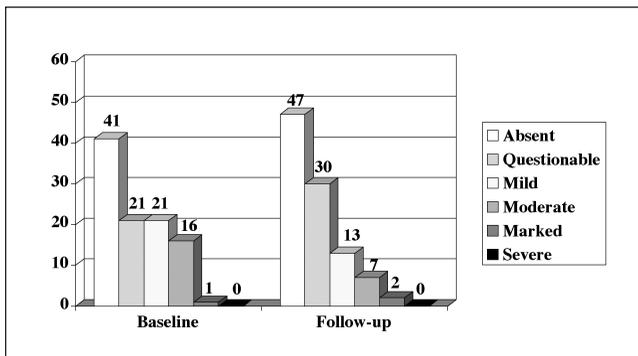
Figure 1. Distribution of BARS Global Item Scores at Baseline (n=146) and Follow-up (n=12) for Basic Education Sites.
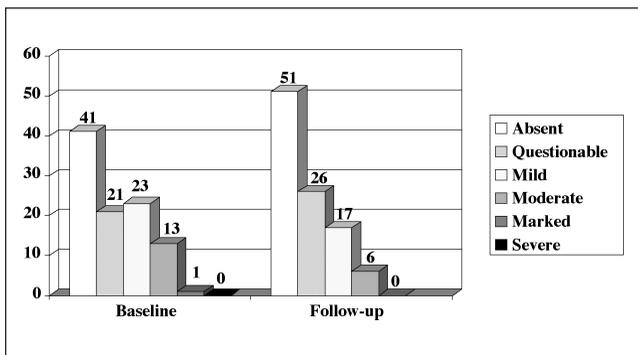
Figure 2. Disribution of BARS Global Item Scores at Baseline (n=145) and Follow-up (n=128) for Enhanced Intervention Sites.
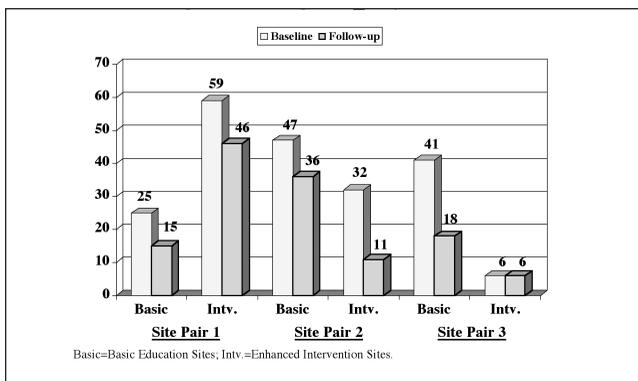
Figure 3. Percent of Patient with Baselne and Follow-up Akathisia Diagnoses (BARS global≥2) by Site/Site Pair.

and both intervention and time effects were significant (P<0.0101). Least square means for site-pair 1 show reductions in akathisia ratings at both basic education and interven-

tion sites (slightly more reduction at the intervention site). Site-pair 2 did not have a significant time by intervention interaction or intervention effect, but did show a significant time effect (P = 0.0017). There was a significant time by intervention effect of BARS global score means at site-pair 3 (P = 0.0232), but in the unexpected direction, with least-square mean change for patients at basic education sites showing significant reductions in akathisia scores, whereas patients at the intervention site showed a slight increase in scores.

Results of the nonparametric ANOVA-type test statistics provided roughly parallel findings to the parametric repeated measures ANOVA results. With the exception of the intervention site at pair 3, the relative effects and 95% confidence intervals for all sites indicate a tendency toward lesser values of BARS scores over time. Briefly, relative effects are a summary measure used in nonparametric ANOVAs.[17] They indicate the tendency of an experimental group's estimated distribution to be lesser or greater than the overall average distribution. A relative effect of <0.50 indicates that a distribution has a tendency to be lesser than the average distribution, while a value of > 0.50 indicates a tendency toward greater values.[17]

Modeling Improvement of BARS Akathisia Diagnosis

Logistic regression results controlling for baseline BARS scores only, showed a significant effect (P = 0.0171) of the intervention

Table 3. Repeated Measures ANOVA and Nonparametric Results by Site-pair (n = 293)

Repeated Measures ANOVA Effects	Site-Pair 1		Site-Pair 2		Site-Pair 3	
	F	P-value	F	P-value	F	P-value
Intervention	6.88	0.0101	2.40	0.1250	18.21	0.0001
Time	6.50	0.0123	10.47	0.0017	0.40	0.5290
Intervention x time	2.99	0.0872	0.09	0.7621	5.32	0.0232
BARS LS Means		(SE)		(SE)		(SE)
Basic sites—baseline	0.85	(0.18)	1.46	(0.17)	1.10	(0.14)
Basic sites—follow-up	0.74	(0.17)	1.05	(0.14)	0.72	(0.12)
Enhanced sites—baseline	1.55	(0.14)	1.23	(0.14)	0.14	(0.17)
Enhanced sites—follow-up	1.02	(0.14)	0.77	(0.12)	0.35	(0.15)
Nonparametric Analysis Effects	Nonpar ATS	P-value	Nonpar ATS	P-value	Nonpar ATS	P-value
Intervention	-2.40	0.1847	1.02	0.3137	5.07	0.0001
Time	2.66	0.0091	3.38	0.0011	-.056	0.9554
Intervention x time	-1.98	0.0496	-0.06	0.9548	2.33	0.0218
Relative Effects		(CI)		(CI)		(CI)
Basic sites—baseline	0.44	(.38-.51)	0.59	(.51-.66)	0.60	(.54-.65)
Basic sites—follow-up	0.43	(.37-.49)	0.47	(.39-.55)	0.54	(.49-.59)
Enhanced sites—baseline	0.61	(.55-.66)	0.54	(.48-.60)	0.36	(.32-.40)
Enhanced sites—follow-up	0.48	(.42-.53)	0.42	(.37-.48)	0.42	(.37-.48)

Note: Nonpar ATS = Nonparametric ANOVA Type Statistic; CI = confidence interval. Odds Ratio

Table 4. Logistic Regression Results Modeling the Absence of BARS Diagnosis at Follow-up by Site-pair (total n = 240)

Parameter	Site-Pair 1			Site-Pair 2			Site-Pair 3		
	Odds Ratio	CI	P-value	Odds Ratio	CI	P-value	Odds Ratio	CI	P-value
Basic versus enhanced sites (controlling for baseline BARS only)	3.20	(0.97-10.50)	0.0556	0.24	(0.07-0.77)	0.0171	0.29	(0.05-1.61)	0.1571
Basic versus enhanced sites (controlling for all covariates via propensity score)	1.96	(0.40-9.56)	0.4041	0.17	(0.03-1.04)	0.0557	0.41	(0.03-5.06)	0.4846

at site-pair 2, and marginally significant effect of the intervention when all covariates were controlled for with propensity scores ($P = 0.0557$)(see Table 4). Site-pairs 1 and 3 showed no significant effects in either logistic model.

Prevalence of Akathisia by Antipsychotic Drug Type and Dose Range

Of the 229 patients classified as receiving only traditional (n = 41) or novel (n = 137) antipsychotic medication at baseline, 44% of those receiving traditional medication had positive BARS akathisia diagnosis at baseline compared with 32% of the patients on novel medications ($\chi^2 = 3.654$, df = 1; $P = 0.056$). At follow-up, there was no significant difference in the frequency of BARS diagnoses for patients receiving novel versus traditional medications; 23% of patients on conventional medications and 24% of patients on novel medications had a positive akathisia diagnosis ($\chi^2 = 0.0602$, df=1; $P = 0.806$). Similarly, at baseline, 47% of patients receiving risperidone versus 21% of patients receiving olanzapine had a positive BARS diagnosis ($\chi^2 = 9.42$, df = 1; $P = 0.002$), but there was no significant difference in akathisia diagnoses at follow-up by drug ($\chi^2 = 1.469$, df = 1; $P = 0.2255$).

No significant association was found between guideline concordant range and BARS diagnosis at either baseline or follow-up. At baseline, 37% of patients receiving antipsychotic medications below or within recommended ranges had a positive BARS diagnosis, versus 39% of those receiving above recommended dose ranges ($\chi^2 = 0.0556$, df = 1; $P = 0.8137$). At follow-up, the percentage of patients with a positive BARS diagnosis had dropped from a total of 38% to 23%. Of those receiving medication within or below recommended ranges, 23% had a positive BARS diagnosis versus 22% of those receiving above recommended dosing ($\chi^2 = 0.0395$, df = 1; $P = 0.8424$).

DISCUSSION

Overall, the findings presented in this study are consistent with other studies showing that akathisia tends to improve over time among veterans being treated for schizophrenia.[22] At baseline, when patients in this sample were assessed as having an acute psychiatric exacerbation, the prevalence of akathisia was slightly higher (38%) than has been found in previous studies (20%-25%), but outcomes measured 6 months later showed rates more consistent with other studies (23%).[1] The results suggest that treatment delivered under both the enhanced and basic education strategy sites reduced akathisia. The baseline and follow-up rates of akathisia were roughly equivalent when comparing all patients at enhanced and basic education sites.

Site-specific analyses of the regionally-matched enhanced and basic education strategy VAMCs, however, add a slightly more complex layer of understanding to the study results. Site analyses of mean BARS global scores revealed that all but 1 of the sites showed improved ratings of akathisia (decrease in mean BARS scores); the site that did not show improvement (pair 3 intervention site) had a minimal increase in BARS global item mean scores over time and a very low prevalence of akathisia diagnoses to begin with (6% at baseline and identical prevalence rate at follow-up). Numerous baseline clinical and demographic differences suggest the sites were not matched well for comparison. Site-pairs 1 and 3 also showed a pattern of time by intervention interaction effect according to both the repeated measures ANOVA and nonparametric analysis, which suggests that change over time in BARS ratings was different by site. In addition, the logistic regression results controlling for baseline akathisia diagnosis (only) revealed a significant intervention effect at site-pair 2, but when patient covariates were added to the model via propensity scores, significance of the intervention was marginal. Taken together, these findings suggest that improvements in akathisia may be due to numerous site-specific or patient characteristics.

The authors also examined the effect of novel versus conventional antipsychotic medications by comparing these groups; study findings were consistent with literature showing a reduced prevalence of akathisia in patients treated with newer atypical antipsychotic medications, and a higher prevalence of akathisia among those with treated with risperidone compared with those treated with olanzapine.[5] Patients who received novel antipsychotic medication had a significantly lower frequency of akathisia at baseline; but akathisia was not significantly related to type of antipsychotic medication at 6-month follow-up.

Though numerous patient factors and covariates were controlled for using the propensity approach, including high antipsychotic dosing, a detailed examination of the potential relationship between all possible medication factors (depot, dosing, medications for side-effects, and akathisia was not conducted in this study. Thus, a limitation of this study is that analyses did not control for side-effect medications. Though side effect medications are potentially important covariates to control for in analyses of akathisia, results suggest that there was not a significant difference in the prevalence of akathisia for patients who were receiving doses above the recommended dosing ranges compared with those within/below the range (at baseline and follow-up time points). Previous studies have shown a relationship between higher doses and akathisia.[23]

The study results are limited in several other respects that should be noted. First the relatively small sample sizes for site-pair analyses limits the power of the analyses. Another potential limitation of this study may be related to the method of administering the BARS, which relied on trained research assistants rather than clinicians. Akathisia can be difficult to distinguish from psychotic agitation even for trained clinicians[24] and because the patients selected for this study were, by definition, experiencing an acute exacerbation of schizophrenia,

RAs may not have been as sensitive in their ratings as experienced clinicians would have been. Finally, the study results are not necessarily generalizable beyond male veterans, and it is not known whether the results are specific only to the geographic regions examined. Several limitations exist due to variation in site facilities; excessive differences in sociodemographic and clinical characteristics created unequal populations at the basic education and enhanced intervention sites, and each facility retained its own RA, which may have introduced differences in BARS ratings. While analyses were done separately by site-pairs to help combat this issue, the complication of poorly matched sociodemographic and clinical characteristics between the sites still remains a problem that could not be completely compensated for in this study by any means of statistical analysis.

Implications for Behavioral Health Services and Research

The results of this study may have implications for procedures used to analyze BARS scores; specifically, using nonparametric methods to analyze BARS global item scores, which are not continuous in nature, but rather ordinal, and often produce skewed distributions due the relatively low prevalence rates of akathisia. In this study, using a parametric model alongside a parallel nonparametric model allowed us to see if conclusions that were reached by the parametric model might have been sensitive to departures from assumptions. This nonparametric approach may be particularly useful for analyzing BARS data and other similarly distributed ratings. The nonparametric approach used by the authors is also appropriate for repeated measures longitudinal study designs. The results of this study also indicate that for patients with schizophrenia experiencing an acute exacerbation, akathisia improved over time, but the enhanced guideline-implementation strategy did not consistently result in lower prevalence and severity of akathisia, apparently

due to considerable differences in patients' clinical and sociodemographic characteristics or other site-specific factors.

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